

What is claimed is:

1. A binding polypeptide, or functional fragment thereof, comprising a k_{on} of at least about $9 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ for associating with a ligand and having therapeutic potency.

2. A grafted antibody, or functional fragment thereof, comprising a k_{on} of at least about $1.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ to a ligand and having therapeutic potency.

3. A human antibody, or functional fragment thereof, comprising a k_{on} of at least about $9 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ to a ligand and having therapeutic potency.

4. A method of determining the therapeutic potency of a binding polypeptide, comprising:

(a) contacting a binding polypeptide with a ligand;

(b) measuring association rate for binding between said binding polypeptide and said ligand, and

(c) comparing said association rate for said binding polypeptide to an association rate for a therapeutic control, the relative association rate for said binding polypeptide compared to said association rate for said therapeutic control indicating that said binding polypeptide will exhibit a difference in therapeutic potency correlative with the difference between said association rates.

5. The method of claim 4, further comprising the step of:

(d) changing one or more amino acids in said binding polypeptide and repeating steps (a) through (c)
5 one or more times.

6. The method of claim 5, wherein said association rate for said changed binding polypeptide increases by at least 4-fold.

7. The method of claim 4, wherein said
10 association rate for said binding polypeptide increases correlative with improved therapeutic potency.

8. The method of claim 4, wherein said association rate for said binding polypeptide is at least 4-fold higher than said association rate for said
15 therapeutic control.

9. The method of claim 4, wherein said association rate is indicated by k_{on} .

10. The method of claim 9, wherein said k_{on} for said binding polypeptide is at least about
20 $8 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$.

11. The method of claim 10, wherein said therapeutic potency correlative with the difference between said k_{on} for said binding polypeptide and said k_{on} for said therapeutic control is independent of an effect
25 of a difference between K_a for said binding polypeptide and K_a for said therapeutic control.

12. The method of claim 10, wherein said difference between said k_{on} for said binding polypeptide and said k_{on} for said therapeutic control is an increase and K_a for said binding polypeptide is a similar value to 5 K_a for said therapeutic control.

13. The method of claim 10, wherein said difference between said k_{on} for said binding polypeptide and said k_{on} for said therapeutic control is an increase and K_a for said binding polypeptide is a lower value than 10 K_a for said therapeutic control.

14. The method of claim 4, wherein said binding polypeptide is selected from the group consisting of a receptor, enzyme, hormone, immunoglobulin, antibody, humanized antibody, human antibody, T-cell receptor, 15 integrin, hormone receptor, lectin, membrane receptor, transmitter receptor, protease, oxidoreductase, kinase, phosphatase, DNA modifying enzyme, transcription factor, GTPase, ATPase, membrane channel, growth factor, insulin, cytokine, neural peptide, extracellular matrix protein 20 and clotting factor, or functional fragments thereof.

15. The method of claim 4, wherein said therapeutic control is selected from the group consisting of a receptor, enzyme, hormone, immunoglobulin, antibody, humanized antibody, human antibody, T-cell receptor, 25 integrin, hormone receptor, lectin, membrane receptor, transmitter receptor, protease, oxidoreductase, kinase, phosphatase, DNA modifying enzyme, transcription factor, GTPase, ATPase, membrane channel, growth factor, insulin, cytokine, neural peptide, extracellular matrix protein 30 and clotting factor, or functional fragments thereof.

16. A method of determining therapeutic potency of a binding polypeptide, comprising:

- (a) contacting two or more binding polypeptides of a population with a ligand;
 - 5 (b) measuring association rates for said two or more binding polypeptides binding to said ligand;
 - (c) comparing said association rates for said two or more binding polypeptides binding to said ligand, and
 - (d) identifying a binding polypeptide
- 10 exhibiting a higher association rate for binding to said ligand than one or more other binding polypeptides of the population, said higher association rate correlating with the therapeutic potency of said identified binding polypeptide.

15 17. The method of claim 16, wherein said higher association rate is 4-fold higher.

18. The method of claim 16, further comprising the step of:

- 20 (d) changing one or more amino acids in said identified binding polypeptide and repeating steps (a) through (c) one or more times.

19. The method of claim 16, wherein said association rate is identified by k_{on} .

20. The method of claim 19, wherein said k_{on} is
25 at least about $1.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$.

21. The method of claim 19, wherein said high k_{on} is larger than k_{on} for a therapeutic control.

22. The method of claim 16, wherein said binding polypeptide is selected from the group consisting of a receptor, enzyme, hormone, immunoglobulin, antibody, humanized antibody, human antibody, T-cell receptor,
5 integrin, hormone receptor, lectin, membrane receptor, transmitter receptor, protease, oxidoreductase, kinase, phosphatase, DNA modifying enzyme, transcription factor, GTPase, ATPase, membrane channel, growth factor, insulin, cytokine, neural peptide, extracellular matrix protein
10 and clotting factor, or functional fragments thereof.

23. A method for producing a binding polypeptide with improved therapeutic potency, comprising:

(a) changing one or more amino acids in a parent polypeptide to produce one or more different progeny polypeptides;
15 (b) measuring the association rate for said one or more different progeny polypeptides associating with a ligand, and
(c) identifying a binding polypeptide from said
20 one or more progeny polypeptides having at least a 4-fold increase in association rate to a ligand compared to the parent polypeptide, said increased association rate resulting in improved therapeutic potency toward a pathological condition.

25 24. The method of claim 23, wherein said association rate is indicated by k_{on} .

25. The method of claim 24, wherein said increased k_{on} is at least about $3 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$.

26. The method of claim 24, wherein said increase in k_{on} resulting in improved therapeutic potency is independent of an effect of a change in K_a for said binding polypeptide.

5 27. The method of claim 24, wherein said binding polypeptide having at least a 4-fold increase in k_{on} has a K_a value similar to K_a for said parent polypeptide.

10 28. The method of claim 24, wherein said binding polypeptide having at least a 4-fold increase in k_{on} has a K_a value lower than K_a for said parent polypeptide.

15 29. The method of claim 23, wherein said binding polypeptide is selected from the group consisting of a receptor, enzyme, hormone, immunoglobulin, antibody, humanized antibody, human antibody, T-cell receptor, integrin, hormone receptor, lectin, membrane receptor, transmitter receptor, protease, oxidoreductase, kinase, phosphatase, DNA modifying enzyme, transcription factor, GTPase, ATPase, membrane channel, growth factor, insulin, cytokine, neural peptide, extracellular matrix protein
20 and clotting factor, or functional fragments thereof.

30. The method of claim 23, wherein said parent polypeptide is selected from the group consisting of a receptor, enzyme, hormone, immunoglobulin, antibody, humanized antibody, human antibody, T-cell receptor,
5 integrin, hormone receptor, lectin, membrane receptor, transmitter receptor, protease, oxidoreductase, kinase, phosphatase, DNA modifying enzyme, transcription factor, GTPase, ATPase, membrane channel, growth factor, insulin, cytokine, neural peptide, extracellular matrix protein
10 and clotting factor, or functional fragments thereof.

31. A method for producing a binding polypeptides with improved therapeutic potency, comprising:

- (a) changing one or more amino acids in a parent polypeptide to produce one or more different progeny polypeptides;
- (b) measuring the association rate for said one or more different progeny polypeptides associating with a ligand, and
- (c) identifying a binding polypeptide from said 20 one or more different progeny polypeptides having a k_{on} of at least about $1.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ for binding polypeptide associating with a ligand, said binding polypeptide having improved therapeutic potency.

32. The method of claim 31, wherein said k_{on} is
25 at least about $9 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$.

33. The method of claim 31, wherein said binding polypeptide is selected from the group consisting of a receptor, enzyme, hormone, immunoglobulin, antibody, humanized antibody, human antibody, T-cell receptor,
5 integrin, hormone receptor, lectin, membrane receptor, transmitter receptor, protease, oxidoreductase, kinase, phosphatase, DNA modifying enzyme, transcription factor, GTPase, ATPase, membrane channel, growth factor, insulin, cytokine, neural peptide, extracellular matrix protein
10 and clotting factor, or functional fragments thereof.

34. The method of claim 31, wherein said parent polypeptide is selected from the group consisting of a receptor, enzyme, hormone, immunoglobulin, antibody, humanized antibody, human antibody, T-cell receptor,
15 integrin, hormone receptor, lectin, membrane receptor, transmitter receptor, protease, oxidoreductase, kinase, phosphatase, DNA modifying enzyme, transcription factor, GTPase, ATPase, membrane channel, growth factor, insulin, cytokine, neural peptide, extracellular matrix protein
20 and clotting factor, or functional fragments thereof.

35. A method of treating a pathological condition, comprising administering an effective amount of a binding polypeptide comprising a k_{on} of at least about $9 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ for associating with a ligand.

36. The method of claim 35, wherein said binding polypeptide is selected from the group consisting of a receptor, enzyme, hormone, immunoglobulin, antibody, humanized antibody, human antibody, T-cell receptor,
5 integrin, hormone receptor, lectin, membrane receptor, transmitter receptor, protease, oxidoreductase, kinase, phosphatase, DNA modifying enzyme, transcription factor, GTPase, ATPase, membrane channel, growth factor, insulin, cytokine, neural peptide, extracellular matrix protein
10 and clotting factor, or functional fragments thereof.